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(54) Title: SUBSTITUTED BENZIMIDAZOLES, PROCESS FOR THEIR PREPARATION AND THEIR PHARMACEUTICAL USE			
<p>(57) Abstract</p> <p>The novel compounds of formula (I), wherein R¹ and R², which are different, is each H, alkyl containing 1-4 carbon atoms or -C(O)-R⁶; one of R¹ or R² is always selected from the group -C(O)-R⁶; wherein R⁶ is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms, R³ is the group -CH₂OCOOR⁷, wherein R⁷ is alkyl containing 1-6 carbon atoms or benzyl; R⁴ and R⁵ are the same or different and selected from -CH₃, -C₂H₅, (a), (b) and -CH₂CH₂OCH₃, or R⁴ and R⁵ form together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by R⁴ and R⁵ is -CH₂CH₂CH₂-, -CH₂CH₂- or -CH₂- as well as pharmaceutical compositions containing such compounds as active ingredient, and the use of the compounds in medicine.</p>			

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Substituted benzimidazoles, process for their preparation and their pharmaceutical use

5

DESCRIPTION

Field of the invention

- 10 The object of the present invention is to provide novel compounds, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer.
- 15 The present invention also relates to the use of the compounds of the invention for inhibiting gastric acid secretion in mammals including man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis, and Zollinger-Ellison syndrome.
- 20 Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compounds of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout.
- 25 The compounds may also be useful in the treatment of diseases related to bone metabolism disorders as well as

the treatment of glaucoma. The invention also relates to pharmaceutical compositions containing the compounds of the invention, as active ingredient. In a further aspect, the invention relates to processes for preparation of such 5 new compounds and to the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

It is a specific primary object of the invention to 10 provide compounds with a high level of bioavailability. The compounds of the invention will also exhibit good stability properties at neutral and acidic pH and a good potency in regard to inhibition of gastric acid secretion. The compounds of the invention will not block 15 the uptake of iodine into the thyroid gland. It has earlier been disclosed in several lectures from the company, where the inventors are working that thyroid toxicity depends on if the compounds are lipophilic or not. The inventors have now unexpectedly found that it is 20 not the lipophilicity that is the critical parameter. The claimed compounds, which include rather hydrophilic compounds, do not give any thyroid toxic effect and have at the same time high acid secretion inhibitory effect, good bioavailability and stability.

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Prior art and background of the invention

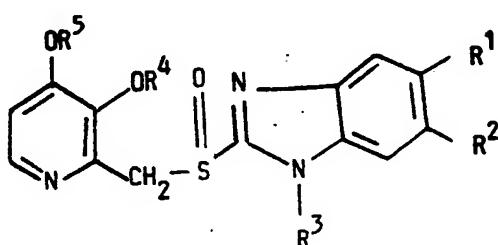
Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents.

30 Among these can be mentioned GB 1 500 043, GB 1 525 958, US 4 182 766, US 4 255 431, US 4 599 347, BE 898 880, EP 124 495, EP 208 452, EP 221 041, EP 279 149, EP 176 308 and Derwent abstract 87-294449/42. Benzimidazole derivatives proposed for use in the treatment or 35 prevention of special gastrointestinal inflammatory diseases are disclosed in US 4 359 465.

The invention

5 The compounds of the formula I are effective as
 10 inhibitors of gastric acid secretion in mammals including
 man and in addition do not block the uptake of iodine
 into the thyroid gland. It has also been found that the
 compounds of the following formula I show high
 bioavailability. Further, the compounds of the invention
 15 exhibit a high chemical stability in solution at neutral
 and acidic pH. The high chemical stability also at acidic
 pH makes the compounds useful for non-enteric coated
 peroral formulations.

20 15 The compounds of the invention are of the following
 formula I:

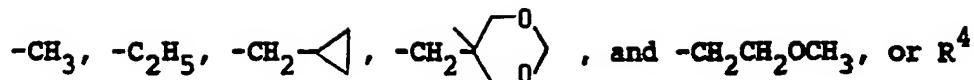


25 wherein
 25 R^1 and R^2 , which are different, is each H, alkyl
 containing 1-4 carbon atoms or $-C(O)-R^6$, one of R^1 or R^2
 is always selected from the group $-C(O)-R^6$;

30 wherein
 30 R^6 is alkyl containing 1-4 carbon atoms or alkoxy
 containing 1-4 carbon atoms

35 R^3 is the group $-CH_2OCOOR^7$, wherein R^7 is alkyl containing
 1-6 carbon atoms or benzyl;

35 R^4 and R^5 are the same or different and selected from



and R^5 form together with the adjacent oxygen atoms

5 attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by R^4 and R^5 is $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}_2-$.

It should be understood that the expressions "alkyl" and

10 "alkoxy" include straight and branched structures.

The structural isomers of the invention described in examples 1-6 may be used separately, or in equal or unequal mixtures.

15

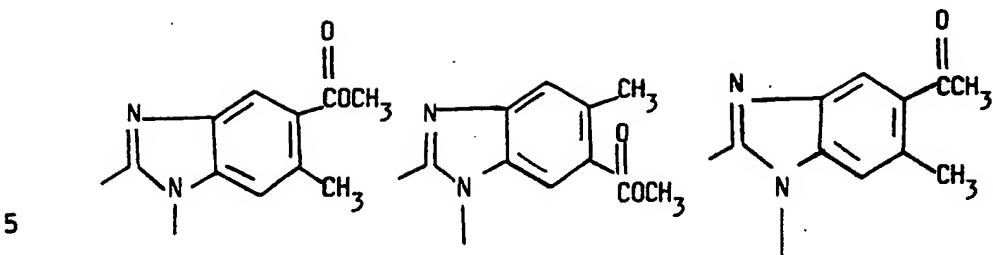
The compounds of the invention of the formula I have an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers) or if they also contain one or more asymmetric carbon atoms, the compounds have two or

20 more diastereomeric forms, each existing in the two enantiomeric forms. Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are within the scope of the present invention. It should also be understood that all the diastereomeric 25 forms possible (pure enantiomers or racemic mixtures) are within the scope of the invention.

Preferred groups of compounds of the formula I are:

30 1. Compounds, wherein R^3 is $-\text{CH}_2\text{OCOOCH}_2\text{CH}_3$.
 2. Compounds, wherein R^1 and R^2 are selected from H, methyl or $-\text{C}(\text{O})-\text{R}^6$, wherein R^6 is alkyl containing 1-4 carbon atoms.
 35 3. Especially preferred benzimidazole structures are:

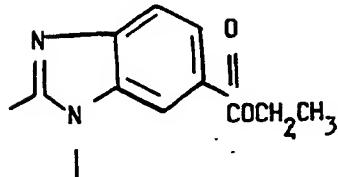
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20 4. Especially preferred are compounds, wherein R^4 and R^5 are methyl.

5. Especially preferred specific compounds of the invention are the compounds listed in the following tabulation

25

R^1	R^2	R^3	R^4	R^5
CH_3	$C(O)OCH_3$	$CH_2OCOOCH_2CH_3$	CH_3	CH_3
$C(O)OCH_3$	CH_3	$CH_2OCOOCH_2CH_3$	CH_3	CH_3
CH_3	$C(O)CH_3$	$CH_2OCOOCH_2CH_3$	CH_3	CH_3
$C(O)CH_3$	CH_3	$CH_2OCOOCH_2CH_3$	CH_3	CH_3

35

It is believed that compounds of formula I are metabolized

into the corresponding compounds, wherein R^3 is H before exerting their effect.

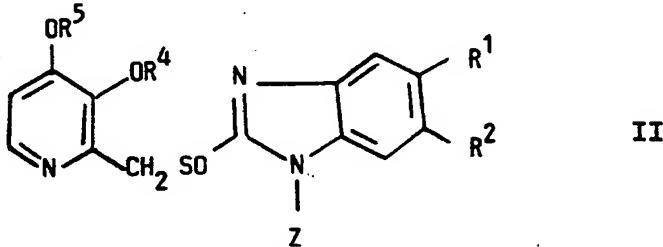
Preparation

5

The compounds of the invention may be prepared according to the following methods:

a) Reacting a compound of the formula II

10



15

wherein R^1 , R^2 , R^4 and R^5 are as defined under formula I, and Z , is either a metal cation such as Na^+ , K^+ , Li^+ or Ag^+ or a quaternary ammonium ion, such as tetrabutylammonium with alkyl chloromethyl carbonate or benzyl chloromethyl carbonate.

20

b) Reacting a compound of the formula II, wherein R^1 , R^2 , R^4 and R^5 are as defined under formula I and Z is hydroxymethyl with a compound of the formula III,

25



30

wherein R^7 is as defined above and X is Cl or imidazole or p -nitrophenoxyl or a functionally equivalent group, in the presence of a suitable base such as triethylamine.

The reactions according to a) and b) are suitably carried out under protective gas in absence of water. Suitable

solvents are hydrocarbons such as toluene or benzene or

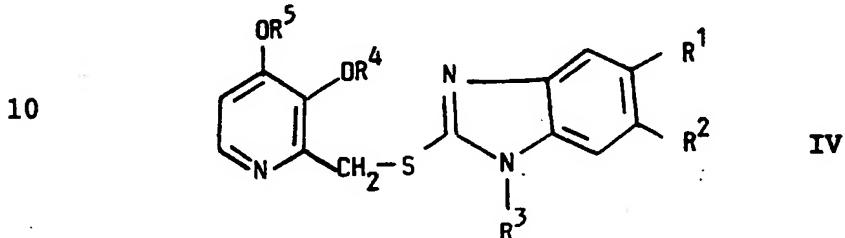
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halogenated hydrocarbons such as methylene chloride or

chloroform, or acetone, acetonitrile or dimethylformamide. The reactions may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture.

5

c) Oxidizing a compound of the formula IV



15 wherein R¹, R², R³, R⁴ and R⁵ are as defined under formula I.

This oxidation may be carried out by using an oxidizing agent such as nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, 20 ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2.2.2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, 25 chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers, ketones.

The oxidation may also be carried out enzymatically by 30 using an oxidizing enzyme or microbiotically by using a suitable microorganism. The structural isomers obtained, may be separated by means of crystallization or chromatography.

35 Racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active

solvent. In the case of racemic diastereomeric mixtures these may be separated into diastereomeric pure enantiomers by means of chromatography or fractional crystallization.

5 The starting materials utilized in the methods a)-c) are in some cases unknown. These unknown starting materials may, be obtained according to processes known per se.

Alkyl chloromethyl carbonate and benzyl chloromethyl
10 carbonate may be obtained from the pertinent alcohol by treatment with chloromethyl chloroformate in the presence of pyridine.

15 Intermediates of the formula II, wherein Z is hydroxymethyl are obtained by reaction of the corresponding benzimidazole compound carrying H in the N-1 position with formaldehyde.

Starting materials of the formula III may be obtained by known methods, e.g. from an alcohol HOR⁷ by treatment with
20 phosgene or 1,1¹-carbonyldiimidazole or p-nitrophenyl chloroformate.

For clinical use a compound of the invention is formulated into pharmaceutical formulations for oral, rectal, or other
25 modes of administration. The pharmaceutical formulation contains a compound of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further
30 object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, and between 1-50% by weight in preparations for oral administration.

35 In the preparation of pharmaceutical formulations containing a compound of the present invention in the form

of dosage units for oral administration a compound selected may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another 5 suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like, as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol 10 waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among 15 pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a 20 suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

25 Soft gelatine capsules may be prepared with capsules containing a mixture of an active compound of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine 30 capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopection, cellulose 35 derivatives or gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain an active substance mixed with a neutral fat base, or they may be prepared in

- 5 the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro
- 10 enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or

- 15 suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents,
- 20 flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

25

The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral dosages will be in the range

- 30 of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Preparation of 5-carbomethoxy-6-methyl-2-[[[(3,4-

- 35 dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-

[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

5 To a suspension of 0.45 g (1.1 mmol) of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole and 0.25 g (1.8 mmol) of potassium carbonate anhydrous in 45 ml of dry acetonitrile, 0.21 g (1.5 mmol) of chloromethyl ethyl carbonate dissolved in 5 ml of acetonitrile was added. The reaction mixture was stirred at room temperature over night. The solvent was then removed in vacuo and the residue was diluted with methylene chloride and water. The organic solvent was dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave the crude product, which was chromatographed with silica gel and eluted with ethyl acetate to provide 0.94 g of a yellow oil which slowly crystallized. Recrystallization with ethanol yielded 0.25 g (44 %) of the title compounds as an isomeric mixture.

10 20 NMR data for the products are given below.

Example 2. Preparation of 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

25 The title compound was obtained by crystallizing the isomeric mixture given in example 1 from ethanol. NMR data are given below.

30 Example 3. Preparation of 5-acetyl-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-acetyl-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

35 To a magnetically stirred suspension of potassium carbonate

anhydrous (0.48 g, 3.47 mmol) in 80 ml of dry acetonitrile 0.80 g (2.14 mmol) of 5-acetyl-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and 0.39 g (2.8 mmol) of chloromethyl ethyl carbonate dissolved in 10 5 ml of acetonitrile was added dropwise. Stirring was continued at room temperature for 20 hours. The solvent was removed in vacuo, the residue diluted with methylene chloride, the methylene chloride solution washed with water and dried over anhydrous sodium sulfate. Removal of the 10 solvent in vacuo gave the crude product which was chromatographed with silica gel and eluted with ethyl acetate to give 0.63 g of an almost white crystalline solid. The product was recrystallized from ethyl acetate to give 0.50 g (49 %) of the title compounds as an isomeric 15 mixture.

NMR data for the products are given below.

Example 4. Preparation of 5-acetyl-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

The title compound was isolated from the isomeric mixture given in example 3 by chromatography on a silica column with methylene chloride - acetonitrile (ratio 6:4) as eluent. The 25 title compound was crystallized from ethanol. NMR data are given below.

Example 5. Preparation of 6-acetyl-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

The title compound was isolated from the isomeric mixture given in example 3 by chromatography on a silica column with methylene chloride-acetonitrile (ratio 6:4) as eluent. The 35 title compound was crystallized from ethanol. NMR data are given below.

Example 6 Preparation of 5-carbethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

To a suspension of 0.28 g (0.72 mmol) 5-carbethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole and 10 0.16 g (1.2 mmol) anhydrous potassium carbonate in 20 ml of dry acetonitrile 0.16 g (1.2 mmol) chloromethyl ethyl carbonate dissolved in 2 ml dry acetonitrile was added. The mixture was stirred at ambient temperature over night. The solvent was evaporated off and the crude product was 15 chromatographed on a silica column using ethyl acetate as eluent. Crystallizing from ethanol gave the title compounds as an isomeric mixture, (0.13 g, 37%).

NMR data for the products are given below.

20 Table 1

<u>Ex.</u>	<u>Solvent</u>	<u>NMR data δ ppm</u>
1	CDCl ₃ , (300 MHz)	1.20-1.30 (m, 3H), 2.70 (s, 1.8H), 2.75 (s, 1.2H), 3.85-3.95 (m, 9H), 4.15-4.25 (m, 2H), 4.85-5.05 (m, 2H), 6.40-6.55 (m, 2H), 6.75 (d, 1H), 7.45 (s, 0.6H), 7.65 (s, 0.4 H), 8.10 (d, 1H), 8.20 (s, 0.4 H), 8.40 (s, 0.6 H).
2	CDCl ₃ , (300 MHz)	1.30 (t, 3H), 2.70 (s, 3H) 3.90 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.25 (q, 2H), 4.95 (d, 1H), 5.05 (d, 1H), 6.50 (m, 2H), 6.75 (d, 1H), 7.65 (s, 1H), 8.10 (d, 1H), 8.20 (s,
35		

14

1H)

3	CDCl ₃ (300 MHz)	1.30 (t, 3H) 2.60-2.70 (m, 6H), 3.85-3.90 (m, 6H), 4.25 (q, 2H), 4.85-5.05 (m, 2H), 6.75 (d, 1H), 7.45 (s, 0.7 H), 7.60 (s, 0.3H), 8.05 (s, 0.3H), 8.10 (d, 1H), 8.20 (s, 0.7H)
5		
4	CDCl ₃ (300 MHz)	1.30 (t, 3H), 2.60 (s, 3H), 2.70 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.20 (q, 2H), 4.90 (d, 1H), 5.05 (d, 1H), 6.50 (m, 2H), 6.80 (d, 1H), 7.50 (s, 1H), 8.15 (d, 1H), 8.20 (s, 1H)
10		
15		
5	CDCl ₃ (300 MHz)	1.30 (t, 3H), 2.60 (s, 3H), 2.70 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.25 (q, 2H), 4.90 (d, 1H), 5.05 (d, 1H), 6.55 (m, 2H), 6.80 (d, 1H), 7.60 (s, 1H), 8.05 (s, 1 H), 8.15 (d, 1H)
20		
6	CDCl ₃ (300 MHz)	1.30 (m, 3H), 1.45 (m, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.25 (m, 2H), 4.45 (m, 2H), 5.00 (m, 2H), 6.55 (m, 2H), 6.80 (d, 1H), 7.70 (d, 0.55H), 7.80 (d, 0.45H), 8.10 (m, 2H), 8.35 (s, 0.45H), 8.50 (d, 0.55H).
25		
30		

Preparation of intermediatesExample I 1

5 Preparation of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-carbomethoxy-6-methyl-2-mercpto-1H-benzimidazole (0.67 g, 0.003 mol) and NaOH (0.12 g, 0.003 mol) in H₂O (0.6 ml) 10 were dissolved in CH₃OH (15 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride, (=0.0036 mol) as a crude material in CH₃OH (10 ml) and NaOH (0.144 g, 0.0036 mol) in H₂O (0.72 ml) were added. The mixture was heated to reflux and the reflux was continued for 1 hour. CH₃OH was 15 evaporated off and the crude material was purified by chromatography on a silica column using CH₂Cl₂-CH₃OH (98-2) as eluent, giving (1.03 g, 92%) of the pure title compound.

NMR data are given below.

20

Example I 2

Preparation of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

25

5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (1.03 g, 0.00276 mol) was dissolved in CH₂Cl₂ (30 ml). NaHCO₃ (0.46 g, 0.0055 mol) in H₂O (10 ml) was added and the mixture was 30 cooled to +2°C. m-chloroperbenzoic acid 69.5% (0.62 g, 0.0025 mol) dissolved in CH₂Cl₂ (5 ml) was added dropwise under stirring. Stirring was continued at +2°C for 15 min. After separation the organic layer was extracted with an aqueous 0.2 M NaOH solution (3x15 ml, 0.009 mol). After 35 separation the aqueous solutions were combined and neutralized with methyl formate (0.56 ml, 0.009 mol) in the

presence of CH_2Cl_2 (25 ml). After separation the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN (10 ml) giving the title compound (0.68 g, 70%).

5

NMR data are given below.

Example I 3

10 Preparation of 5-acetyl-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-acetyl-6-methyl-2-mercaptop-1H-benzimidazole (4.2 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in H_2O (1 ml) were dissolved 15 in 60 ml ethanol. 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (\approx 17 mmol) as a crude material was added and the mixture was heated to boiling. NaOH (0.7 g, 17 mmol) in H_2O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was 20 diluted with methylene chloride and water. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Crystallizing from acetonitrile gave the title compound, (3.75 g, 62%).

25 NMR data are given below.

Example I 4

30 Preparation of 5-acetyl-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-acetyl-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.75 g, 10 mmol) was dissolved in CH_2Cl_2 (70 ml). NaHCO_3 (1.76 g, 21 mmol) in 35 H_2O (25 ml) was added and the mixture was cooled to \approx +3°C. m-Chloroperbenzoic acid 69.5% (2.43 g, 9.8 mmol) dissolved

in CH_2Cl_2 (20 ml) was added dropwise under stirring. Stirring was continued for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from 5 CH_3CN giving the title compound (2.25 g, 60%).

NMR data are given below.

Example I 5

10

Preparation of 5-carbethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-carbethoxy-2-mercaptop-1H-benzimidazole (2.0 g, 9 mmol) and 15 NaOH (0.36 g, 9 mmol) in H_2O (1 ml) were dissolved in ethanol (30 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (\approx 6.6 mmol) as a crude material were added and the mixture was heated to boiling. NaOH (0.26 g, 6.6 mmol) in H_2O (1 ml) was added and the reflux was continued for 6 20 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. Crystallizing from CH_3CN gave the desired product (1.75 g, 71%).

25

NMR data are given below.

Example I 6

30 **Preparation of 5-carbethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole**

5-carbethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (95.2% pure) (1.4 g, 0.0036 mol) was 35 dissolved in CH_2Cl_2 (30 ml). NaHCO_3 (0.6 g, 0.0072 mol in H_2O (10 ml) was added and the mixture was cooled to $+2^\circ\text{C}$.

m-Chloroperbenzoic acid 69.5 % (0.87 g, 0.0035 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring. Stirring was continued at $+2^\circ\text{C}$ for 10 min. The phases were separated and the organic phase was dried over 5 Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN (15 ml) giving the title compound (0.76 g, 54 %).

NMR data are given below.

10

Table 2

Ex	Solvent	NMR data δ ppm
15	CDCl_3 (300 MHz)	2.70 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 4.40 (s, 2H), 6.90 (d, 1H), 7.35 (s, 1H), 8.20 (s, 1H), 8.25 (d, 1H).
20	CDCl_3 (500 MHz)	2.70 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.8 (d, 1H), 7.30 (b, 1H), 8.20 (d, 1H), 8.35 (b, 1H).
25	CDCl_3 (300 MHz)	2.60 (s, 3H), 2.65 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.35 (s, 2H), 6.85 (d, 1H), 7.25 (s, 0.6H), 7.40 (s, 0.4H), 7.85 (s, 0.4H), 8.05 (s, 0.6H), 8.30 (m, 1H)
30	CDCl_3 (300 MHz)	2.60 (s, 6H), 3.85 (s, 3H), 3.85 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.80 (d, 1H), 7.30 (b, 1H), 8.15 (d, 1H), 8.20 (b, 1H)
35		

19

I 5 CDCl_3
(300 MHz)

1.40 (m, 3H), 3.90 (s, 3H), 3.90
(s, 3H), 4.40 (m, 4H), 6.90
(dd, 1H), 7.45 (d, 0.4H), 7.60
(d, 0.6H), 7.90 (m, 1H), 8.20
(s, 0.6H), 8.25 (m, 1H), 8.25
(s, 0.4H)

5

10 I 6 CDCl_3
(300 MHz)

1.45 (t, 3H), 3.85 (s, 3H),
3.90 (s, 3H), 4.40 (q, 2H),
4.65 (d, 1H), 4.40 (d, 1H),
6.80 (d, 1H), 7.50 7.80 (b, 1H),
8.05 (d, 1H), 8.20 (d, 1H),
8.25, 8.55 (b, 1H)

15

The best mode of carrying out the invention known at present
is to use the compound mixture according to Example 3 and
the compound according to Example 4.

Table 3

Examples of compounds included in the formula I are given in the following table.

Example	R ¹	R ²	R ³	R ⁴	R ⁵	Yield %	Ident. data	Re-marks
1	C(O)OCH ₃ CH ₃	CH ₃ C(O)OCH ₃	CH ₂ OOCOC ₂ H ₅	CH ₃	CH ₃	44	NMR	Isomeric mixture
2	CH ₃	C(O)OCH ₃	CH ₂ OOCOC ₂ H ₅	CH ₃	CH ₃		NMR	Isolated isomer
3	C(O)CH ₃ CH ₃	CH ₃ C(O)CH ₃	CH ₂ OOCOC ₂ H ₅	CH ₃	CH ₃	49	NMR	Isomeric mixture 20
4	C(O)CH ₃	CH ₃	CH ₂ OOCOC ₂ H ₅	CH ₃	CH ₃		NMR	Isolated isomer
5	CH ₃	C(O)CH ₃	CH ₂ OOCOC ₂ H ₅	CH ₃	CH ₃		NMR	Isolated isomer
6	C(O)OCH ₂ CH ₃ H	H	CH ₂ OOCOC ₂ H ₅	CH ₃	CH ₃	37	NMR	Isomeric mixture
		C(O)OCH ₂ CH ₃						

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

5

A compound according to Example 4	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
10 Tween	1.0 g
Flavouring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

15 A solution of the compound mixture according to Example in ethanol and Tween was prepared. Sugar and saccharine were dissolved in 60 g of warm water. After cooling the solution of the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Tablets

25 A tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound mixture according to Example 3	500 g
30	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
35	Distilled water	q.s.

II	Hydroxypropyl methylcellulose	36 g
	Polyethylene glyco	19 g
	Colour Titanium dioxide	4 g
5	Purified water	313 g

I Compound mixture according to Example 3, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was 10 forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a 15 tabletting machine using 7 mm diameter punches.

II A solution of hydroxypropyl methylcellulose and polyethylene glycol in purified water was prepared. After dispersion of titanium dioxide the solution was sprayed 20 onto the tablets I in an Accela Cota^R, Manesty coating equipment. A final tablet weight of 125 mg was obtained.

Capsules

25 Capsules containing 30 mg of active compound were prepared from the following ingredients:

	A compound according to Example 4	300 g
	Lactose	700 g
30	Microcrystalline cellulose	40 g
	Hydroxypropyl cellulose low-substituted	62 g
	Purified water	q.s.

The active compound mixture was mixed with the dry 35 ingredients and granulated with a solution of disodium

hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

5 500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 600 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:
Coating solution:

10	Hydroxypropyl methylcellulose phthalate	70 g
	Cetyl alcohol	4 g
	Acetone	600 g
	Ethanol	200 g

15 The final coated pellets were filled into capsules.

Suppositories

20 Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

25	Compound mixture according to Example 4	4 g
	Witepsol H-15	180 g

The active compound mixture was homogenously mixed with Witepsol H-15 at a temperature of 41°C. The molten mass was volume filled into pre-fabricated suppository packages 30 to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Biological EffectsBioavailability

5

Bioavailability, is assessed by calculating the quotient between the areas under plasma concentration (AUC) curve of a compound of the formula I wherein R³ is hydrogen (herein defined as compound A), following 1) intraduodenal (id) or oral (po) administration of the corresponding compound according to the invention and 2) intravenous (iv) administration of compound A, from the rat and the dog. Low, therapeutically relevant doses, were used. Data are provided in Table 4.

15

Potency for inhibition of acid secretion

The potency for inhibition of acid secretion is measured in the female rat orally and in the dog both 20 intraduodenally and orally.

Potency data are provided in Table 4.

Effects on the uptake of iodine into the thyroid gland.

25

The effect of a compound within the invention of the formula I on the uptake of iodine into the thyroid gland is measured as an effect on the accumulation of ¹²⁵I in the thyroid gland of the corresponding compound of the 30 formula I, wherein R³ is hydrogen, that is a metabolized compound of the formula I.

Biological Tests

35 Inhibition of Gastric Acid Secretion in the Conscious Female Rat.

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen), for collection of gastric secretions. A fourteen 5 days recovery period after surgery is allowed before testing is commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed 10 through the gastric cannula, and 6 ml of Ringer-Glucose given s.c. Acid secretion is stimulated with infusion during 2.5 h (1.2 ml/h, s.c.) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions are collected in 30-min 15 fractions. Test substances or vehicle are given orally 120 min before starting the stimulation, in a volume of 5 ml/kg. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output is calculated as the product of titrant volume and concentration. Further 20 calculations are based on group mean responses from 4-7 rats. Percentage inhibition is calculated from absolute rates of acid output. ED₅₀- values are obtained from graphical interpolation on log dose-response curves, or estimated from single-dose experiments assuming a similar 25 slope for all dose-response curves. The results are based on gastric acid secretion during the third hour after drug/vehicle administration.

Bioavailability in the Male Rat.

30 Male adult rats of the Sprague-Dawley strain were used. One day, prior to the experiments, all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous 35 experiments, were also cannulated in the jugular vein.

(Ref. V Popovic and P Popovic, J Appl Physiol 1960;15,727-728). The rats used for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck.

- 5 The rats were housed individually after surgery and were deprived of food, but not water, before administration of the test substances. The same dose (4 μ mol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).
- 10 Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until analysis of the test compound.
- 15 The area under the blood concentration vs time curve, AUC, for the compound A, determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic
- 20 bioavailability (F%) of the compound A following intraduodenal administration of compounds of the invention of formula I was calculated as

$$25 \quad F(\%) = \frac{\text{AUC(Compound A)}_{\text{id(compound of the invention)}}}{\text{AUC(Compound A)}_{\text{iv(Compound A)}}} \times 100$$

Inhibition of Gastric Acid Secretion and Bioavailability
30 in the Conscious Dog

Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a

- 35 Heidenhain-pouch for the collection of gastric secretions.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a 4 h infusion of histamine

- 5 dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle was given orally, id or iv 1 h after starting the histamine infusion, in a volume of 0.5 ml/kg
- 10 body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenhain-pouch dog.
- 15 The acidity of the gastric juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0.
- 20 Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED₅₀-values were obtained by graphical interpolation on log dose - response curves, or estimated from single-dose
- 25 experiments under the assumption of the same slope of the dose-response curve for all test compounds. All results reported are based on acid output 2 h after dosing.

Blood samples for the analysis of test compound

- 30 concentration in plasma were taken at intervals up to 3 h after dosing. Plasma was separated and frozen within 30 min after collection and later analyzed. AUC (area under the plasma concentration - time curve) from time zero to 3 h after dose for compound A, was calculated by the linear trapezoidal rule. The systemic bioavailability (F%) of the
- 35

compound A after oral or id administration of compounds of the invention was calculated as described above in the rat model.

5 Effect on the accumulation of ^{125}I in the thyroid gland

The accumulation of ^{125}I in the thyroid gland was studied in male, Sprague-Dawley rats which were deprived of food for 24 hours before the test. The experimental protocol of

10 Searle, CE et al. (Biochem J 1950; 47:77-81) was followed.

Test substances, suspended in 0.5% buffered (pH 9) methocel, were administered by oral gavage in a volume of 5 ml/kg body weight. After 1 hour, ^{125}I (300kBq/kg, 3ml/kg)

15 was administered by intraperitoneal injection. Four hours after ^{125}I -administration, the animals were killed by CO_2 -asphyxiation and bled. The thyroid gland together with a piece of the trachea was dissected out and placed in a small test tube for the assay of radioactivity in a gamma

20 counter (LKB-Wallac model 1282 Compugamma). Percentage inhibition was calculated according to the formula $100 (1 - T/P)$, where T and P is the mean radioactivity of thyroid glands from animals treated with test agent and placebo (buffered methocel), respectively. The statistical

25 significance for a difference between test agent- and placebo-treated animals was assessed with the Mann-Whitney U-test (two-tailed). $P < 0.05$ was accepted as significant.

Chemical Stability

30

The chemical stability of the compounds of the invention has been followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values.

35 The results in Table 5 show the half life ($t_{1/2}$) at pH 7, that is the time period after which half the amount of the

original compound remains unchanged, and $t_{10\%}$ at pH 2, that is the time period after which 10% of the original compound has decomposed.

5 Results of biological and stability tests

Table 4 and 5 give a summary of the test data available for the compounds of the invention.

Table 4. Biological Test Data

Test compound Example no.	Inhibition of acid secretion, oral administration		Bioavailability F%	Per cent inhibition of 400 μ mol/kg ^{125}I the uptake of ^{125}I in the thyroid gland		
	Dog	Rat		Dog, ED ₅₀ μ mol/kg	Dog	Rat
	Dog	Rat	oral adm	1d adm	1d adm	
1	1.0 ^b)			1.3 ^{a)}	51 ^b)	106
2						0
3	1.5 ^b)	0.9		1.3 ^{a)} 0.8 ^b)	66 ^b)	99
4					35 ^b)	-7
5					50 ^b)	-7
6						-6

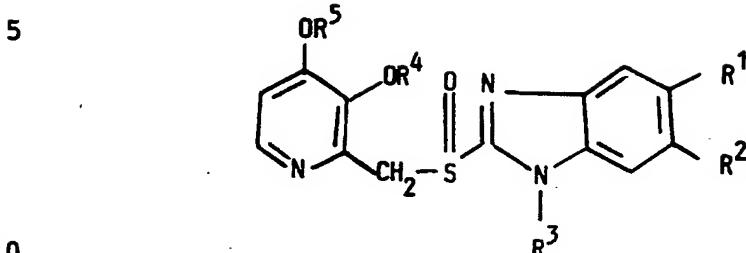
^{a)} gastric fistula dog
^{b)} Heidenhain pouch dog

Table 5, Stability DataTest compound
Example No.Chemical
stability at
pH 7 pH 2
t 1/2 (h) t 10% (h)

1	87	9.5
2	50	6.5
3	51	7.5
4	82	13
5	60	7
6	63	13

CLAIMS:

1. Compounds of the formula I



wherein

15 R^1 and R^2 , which are different, is each H, alkyl containing 1-4 carbon atoms or $-C(O)-R^6$; one of R^1 or R^2 is always selected from the group $-C(O)-R^6$;

15

wherein

20 R^6 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms,

20

R^3 is the group $-CH_2OCOOR^7$, wherein R^7 is alkyl containing 1-6 carbon atoms or benzyl;

25 R^4 and R^5 are the same or different and selected from $-CH_3$,

$-C_2H_5$, $-CH_2\text{C}_2H_5$, $-CH_2\text{CH}_2OCH_3$, or R^4 and R^5

form together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by R^4 and R^5 is $-CH_2CH_2-$

30 CH_2- , $-CH_2CH_2-$ or $-CH_2-$.

2. Compounds according to formula I of claim 1, namely a mixture of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-[(3,4-

dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

3. Compounds according to formula I of claim 1, namely

5 mixture of 5-acetyl-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-acetyl-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

10

4. A compound according to claim 1, namely 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

15

5. A compound according to claim 1, namely 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

20

6. A compound according to claim 1, namely 5-acetyl-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

25

7. A compound according to claim 1, namely 6-acetyl-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

8. A compound according to claim 1, wherein R³ is the group CH₂OCOOCH₂CH₃.

30

9. A compound according to claim 1, wherein R¹ and R² is each H, methyl or -C(O)R⁶, wherein R⁶ is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms.

10. A pharmaceutical composition containing as active

35

ingredient a compound according to claim 1.

11. A compound as defined in claim 1 for use in therapy.

12. A compound as defined in claim 1 for use in inhibiting gastric acid secretion in mammals including man.

5

13. A compound as defined in claim 1 for use in the treatment of gastrointestinal inflammatory diseases in mammals including man.

10 14. A method for inhibiting gastric acid secretion by administering to mammals including man a compound as defined in claim 1.

15 15. A method for the treatment of gastrointestinal inflammatory diseases in mammals including man by administering a compound as defined in claim 1.

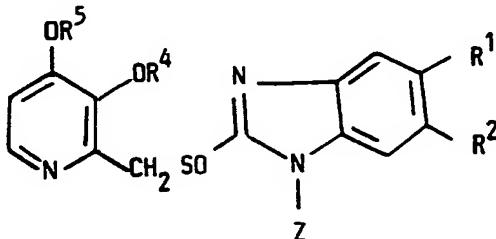
16. Use of a compound according to claim 1 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals including man.

17. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases in mammals including man.

18. A process for the preparation of a compound of the formula I according to claim 1, by
a) reacting a compound of the formula II

30

35

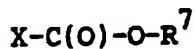


wherein R^1 , R^2 , R^4 and R^5 are as defined under formula I and Z is either a metal cation such as Na^+ , K^+ , Li^+ or Ag^+ or a quaternary ammonium ion, such as tetrabutylammonium with alkyl chloromethyl carbonate or benzyl chloromethyl

5 carbonate or;

b) reacting a compound of the formula II, wherein R^1 , R^2 , R^4 and R^5 are as defined under formula I and Z is hydroxymethyl with a compound of the formula III

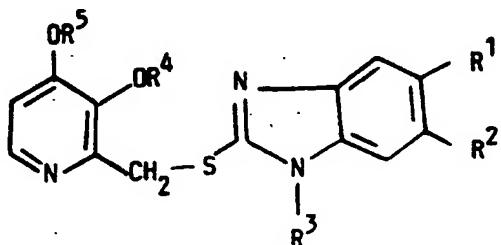
10



wherein R^7 is as defined above and X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group in the 15 presence of a suitable base such as triethylamine or;

c) oxidizing a compound of the formula IV

20

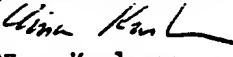


25

wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined under formula I.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00415

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 D 401/12, A 61 K 31/415, 31/44		
II. FIELDS SEARCHED Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	C 07 D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A, 0221041 (AKTIEBOLAGET HÄSSLE) 6 May 1987, see the whole document ---	1-13, 16- 18
A	EP, A, 0176308 (THE UPJOHN COMPANY) 2 April 1986, see the whole document ---	1-13, 16- 18
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
5th September 1991	1991-09-19	
International Searching Authority	Signature of Authorized Officer	
SWEDISH PATENT OFFICE	 Göran Karlsson	

FURTHER INFORMATION, CONTINUED FROM THE SECOND SHEET

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers 14, 15, because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims. It is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.
 No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00415

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on **91-07-31**
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0221041	87-05-06	AU-B-	598491	90-06-28
		AU-D-	6542986	87-05-19
		EP-A-	0233284	87-08-26
		JP-T-	63501151	88-04-28
		US-A-	5021433	91-06-04
		WO-A-	87/02668	87-05-07
EP-A- 0176308	86-04-02	AU-B-	568441	87-12-24
		AU-D-	4669085	86-04-10
		JP-A-	61078784	86-04-22
		US-A-	4873337	89-10-10